Tadler et al. teach well known binding agents that binds lipotechoic acid of gram-positive bacteria.

See Office Action at page 3, lines 1-7. Applicants respectfully traverse this rejection for the reasons set forth below. In particular, this response will show that (1.) the PTO has filed to establish a prima facie case of obviousness; (2.) address the Examiner's arguments; and (3.) show that the Examiner has failed to consider certain secondary considerations.

In order to establish a *prima facie* case of obviousness, the PTO must establish three requirements:

a. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

b. Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

c. Finally, the combination of references must teach or suggest all the limitations of the claims. See In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q 494, 496 (C.C.P.A. 1970).

In this case, the Examiner contends that it would have been *prima facie* obvious to modify the immunoassay taught by Chan by incorporating the set of binding agents taught by McLaughlin and Tadler *et al* because these secondary references disclose antibodies that bind gram negative and gram positive bacteria respectively.

Contrary to the Examiner's assertion, it appears highly unlikely that the skilled artisan would modify Chan's immunoassay using the antibodies disclosed by McLaughlin and Tadler *et al* because the binding agents taught by these secondary references are non-specific. Non-specific binding agents are generally ineffective in diagnostic assays. Chan discloses a diagnostic test and key to the success of the diagnostic test is the use of binding agents that are specific for the infectious agents. In fact, Chan selects binding agents based on their specificity to certain infectious agents. For example, Chan teaches selection of antibodies such as the p41

antibody that differentiates between the purified antigens such as HIV-1 and HIV-2 because "there is minimal cross-reactivity between the two types of antibodies." See page 6.

Furthermore, the Federal Circuit has held that "a proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for the intended purpose." In re Fritch, 972 F.2d at 1265 n.12 (Fed. Cir. 1991). Here, the proposed modification would render Chan's immunoassay inoperable for the intended purpose, i.e., for diagnosing specific infectious agents, because of the lack of specificity of the binding agents taught by Tadler *et al.* and McLaughlin. Moreover, since Chan is completely silent on the use of immobilized binding agents for blood screening purposes a skilled artisan wishing to develop a blood screening assay would not rely upon the teachings of Chan either alone or in combination.

The combination suggested by the Examiner, also fails the second prong of the test; specifically, the skilled artisan would not have a reasonable expectation that such a modified diagnostic test would be effective in determining any specific infectious agent.

Finally, the proposed combination of references fails to meet all the limitations of the claims as required by the law. Specifically, the proposed combination fails to: disclose a method of screening for clinically relevant amounts of bacteria by contacting blood or blood products with a set of binding agents such that blood and blood products found to have an absence of clinically relevant amounts of bacteria is deemed safe for transfer to a recipient.

Accordingly, it is Applicant's position that the PTO has failed to establish a *prima facie* case of obviousness.

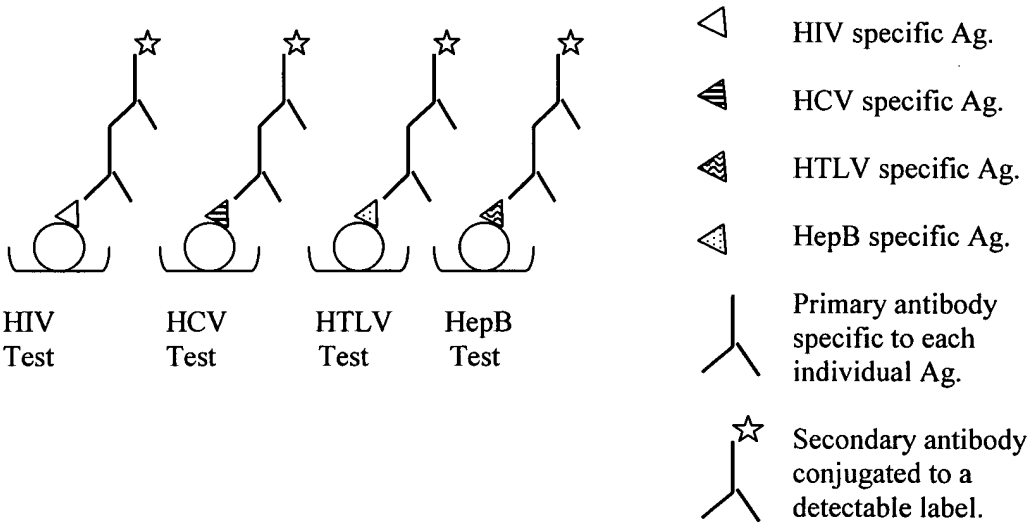
We address below the Examiner's arguments raised in the Office Action dated February 11, 2003:

The Examiner contends that the "feature upon which the applicant relies i.e., one test which indicates the presence of multiple analytes is not recited in the rejected claims." First, for the record, Applicants are not relying on any one distinction from the prior art in establishing non-obviousness of the claimed invention. In determining obviousness, section 103 expressly requires considering the claimed invention "as a whole." Focusing the section 103 inquiry on a particular aspect of the invention that differs from the prior art improperly disregards the statutory mandate of considering the "invention as a whole". The cited difference is but one

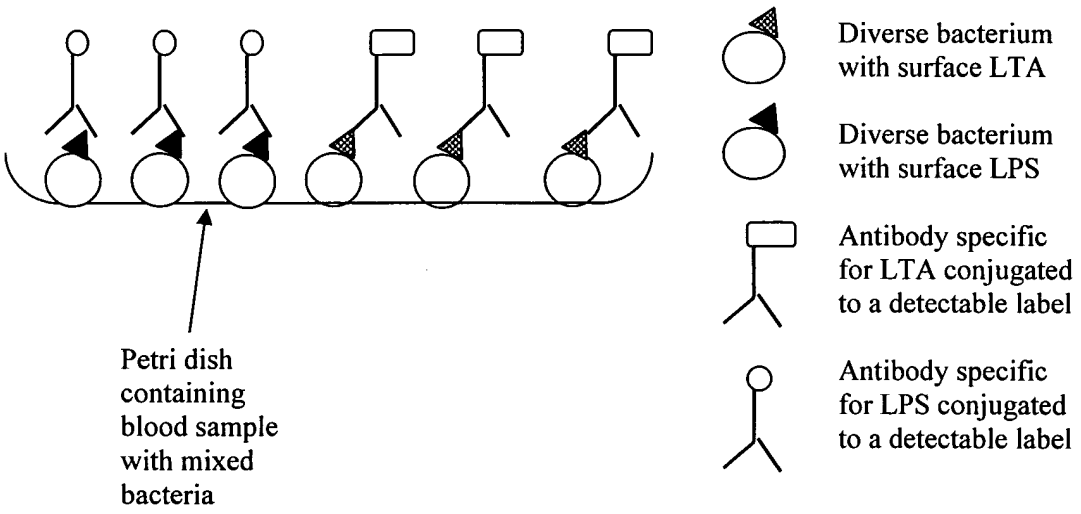
among many differences that have to be taken into account by the PTO when considering the "claimed invention as a whole."

That said, we disagree with the Examiner's characterization that Chan teaches one test. Chan does not teach one test instead Chan teaches multiple discrete tests all conducted simultaneously. A simple illustration shows the differences between the two tests:

Chan et al. (EP 461,462) showing multiple discrete assays for specific infectious agents:



One embodiment of the instant invention: A single assay test for detecting multiple bacterial species.



The Examiner further asserts that "although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims." As discussed above, the instant claims do not rely on any one feature for establishing non-obviousness. Accordingly, it is Applicant's position that no limitations have to be read into the claims in order to establish non-obviousness. Moreover, as sanctioned by current law the claims read in light of the teachings of the specification are non-obvious.

Similarly, the Examiner notes that the pan-generic nature of the claimed binding agents is another difference between the claimed invention and the prior art. The Examiner states that the claimed references meet all the limitations of the claims because they disclose binding agents that can bind gram positive and gram negative bacteria. Applicants respectfully disagree. The cited references do not meet all the limitations of the claims in that they do not anticipate the claimed invention. Furthermore, the cited references do not render the claimed invention obvious to one of ordinary skill in the art.

The Examiner further argues "one cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references." Applicants agree. In this case, not only is Chan deficient in rendering the claimed invention obvious but the combination of references proposed by the Examiner is also legally insufficient in rendering the claimed invention obvious. To reiterate, the cited references are limited in their teachings as follows:

Chan, the primary reference, discloses a diagnostic immunoassay using either immobilized antigens for detecting antibodies generated in a subject in response to an infection or immobilized antibodies for detecting an antigen in a test sample. The immobilized antibodies form complexes with the antigens and the antigen-antibody complexes are then detected. All the examples in this PCT application are directed to the use of immobilized, purified or recombinant antigens of HIV-1, HIV-2, and HCV for detecting the presence of antibodies generated in response to such infection in the blood of a patient. Tadler *et al.* and McLaughlin teach antibodies that bind gram positive or gram negative bacteria. The teachings of Chan taken together with the teachings of the secondary references fail to teach or suggest a method for detecting clinically relevant amounts of bacteria in blood or blood products as required by the

instant claims. In fact, the cited references, either singly or in combination fail on a number of counts:

1.) The cited art fails to disclose or suggest a method of screening blood or blood products for bacterial contaminants.
2.) The cited art fails to teach detection of multiple unknown antigens. For instance, Chan's immunoassay depends on the fact that the skilled artisan knows or suspects that the test sample contains or may contain certain specific antigens or antibodies and their test uses predetermined immobilized binding agents that will bind and detect these known/suspected antigens and/or antibodies. There is no teaching or suggestion in Chan or the secondary references for using a set of binding agents that are capable of binding and detecting a wide range of unknown antigens. In the case of a blood screening assay the skilled artisan has no or little knowledge with regards to the bacterial contaminants that may be present.
3.) The references fail to teach detection of clinically relevant amounts of bacteria in blood or blood products as required by the claims.

As stated above, the cited art singly or in combination fails to render the claimed invention obvious. Furthermore, the skilled artisan would have no motivation to modify the teachings of the references as proposed by the Examiner nor would they expect such a combination to yield an effective diagnostic test or for that matter an effective blood screening protocol.

The Examiner contends Tadler et al. does not teach away from the claimed invention because "disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." Applicants respectfully submit that Tadler et al. fails on two counts: (1.) it is unlikely that a skilled artisan wishing to modify a diagnostic test such as that disclosed by Chan would look to the antibodies described in Tadler as these binding agents are non-specific in nature; and (2) it is unlikely a skilled artisan wishing to screen for clinically relevant amounts of bacteria in blood or blood products would use the antibodies disclosed by Tadler because Tadler discloses that these are ineffective in detecting most bacteremias. It is Applicant's position that the broader disclosure of antibodies that can detect

gram-positive bacteria by itself fails to provide motivation to a skilled artisan wishing to develop a blood screening assay. Taken together with an explicit teaching that these antibodies are ineffective in detecting "most bacteremias" would teach away from such a selection.

Furthermore, Applicants respectfully remind the Examiner that the claims are directed to detecting clinically relevant amounts of bacteria. The specification teaches that "clinically relevant amount" means an amount of bacterial contamination that is equal to or higher than an amount that, when present in blood transfused to a recipient causes any one of the following symptoms in the recipient: fever, nausea/vomiting, chills, hypotension, headache, septic shock, organ failure etc. Typically, a clinically relevant amount is greater than 1×10^7 CFU/ml of blood product. Tadler teaches that the disclosed assay *is not adequate to detect most bacteremias.* Given such an express teaching, it is unlikely that the skilled artisan would select antibodies that are known to be inadequate in screening for clinically relevant amounts of bacteria in blood. The Examiner states "it is noted that the claims do not require the binding agents to detect all of the gram positive bacteria or an entire class of microorganisms." That may be so, however, the claims *do* require screening for clinically relevant amounts of bacteria.

The Examiner argues that the skilled artisan would be motivated to modify the teachings of Chan because the secondary references teach using binding agents that bind gram positive and gram negative bacteria. As discussed above, mere binding to a set of bacterial antigens does not provide sufficient motivation to the skilled artisan to modify the immunoassay taught by Chan. Furthermore, the Examiner argues "applicants have presented no evidence that there was NO reasonable expectation of success." Applicants disagree. The above discussion, shows that the skilled artisan would not have a reasonable expectation that a diagnostic test with non-specific binding agents to be successful, nor would they expect a blood screening assay with agents that are ineffective in detecting most bacteremias would be effective. Additionally, the Examiner's contention flies in the face of the comprehensive list of documents demonstrating the state of the art at the time of filing all showing the need for a blood test for bacterial contaminants and the lack of an effective protocol. Furthermore, the legal basis for Examiner's requirement that Applicants must show that there was "NO reasonable expectation of success" is unclear. Clarification is respectfully requested.

It is Applicant's position that the comprehensive listing of documents provided with the previous response sets forth the state of the art, the critical need for a safe and effective blood screening protocol, and explicit assertions from those skilled in this art that to date no method exists for detecting clinically relevant amounts of bacterial contamination. These documents clearly indicate that those skilled in this art would not have expected the combination of references proposed by the Examiner would provide an effective method for detecting clinically relevant amounts of bacterial contamination in blood.

In particular, Wagner teaches away from developing an immunological-based blood screening assay because he states that there are no common antigens on the surface of the diverse bacterial species. This reference shows that one skilled in this art would not expect an immunological-based test would be effective in detecting clinically relevant amounts of bacterial contamination. The Examiner argues that Wagner's teachings are not persuasive because "the claims only require that a bacterial antigen is detected, not each and every gram negative and gram positive bacterial antigen be detected." Applicants disagree; although the claims do not require that each and every gram negative and gram positive bacterial antigen be detected; the claims do require that clinically relevant amounts of bacterial contamination be detected.

Similarly, Klein et al. provide a summary of an FDA sponsored conference that took place in 1995. The overview includes a description of certain antigen-based detection systems that were being developed by Bionax. This assay was designed to detect peptidoglycans. However, Bionax abandoned the test due to its inability to detect clinically relevant amounts of bacteria since peptidoglycans are not expressed on the surface of gram-negative bacteria. The Examiner dismisses Klein et al as teaching the use of chemi-luminescent methods that are not being claimed. In contrast, Klein et al. provides a summary of the state of the art of blood screening and shows that there was no viable blood screening assay for bacterial contamination as of 1996.

In addition, to demonstrating lack of a reasonable expectation that immunological-based method would be successful for blood screening purposes, the listed publications show the long-felt need in the art for such a test. In In re Mahurkar, 831 F.Supp. 1354, 1377-78 (N.D.Ill. 1993), *aff'd*, 71 F.3d 1573 (Fed. Cir. 1995), Judge Easterbrook stated:

> The existence of an enduring, unmet need is strong evidence that the invention is novel, not obvious, and not anticipated. If people are clamoring for a solution, and the best minds do not find it for years, that is practical evidence –the kind that can't be bought from a hired expert, the kind that does not depend on fallible memories or doubtful inferences—of the state of the knowledge.

The Federal Circuit addressed the issue of long-felt need and the failure of others in Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044 (Fed. Cir. 1988):

> The [district] court also did not take into account other objective evidence of long felt need and failure of others. The Maryland study, by itself, is strong evidence of both. The fact that such an extensive study was performed in 1953 shows a significant interest in drag reduction techniques long before fuel consumption became a critical concern. In addition, the record does not contain any indication that in the approximately ten years between the Maryland study and Saunders' invention any solution to the air resistance problem of tractor-trailers was forthcoming, particularly a solution of such effectiveness, and of such ease of use and manufacture, as the claimed invention.
>
> The district court did not consider the failure of the Maryland study to produce an effective solution to the wind resistance problem as an indication of long felt need. Instead, it viewed that failure as an indication that a later invention, based on a different principle, would have been obvious, because the inventor would know from such failure that he should try some other approach. Under this reasoning, it would be progressively more difficult, after a succession of failures, to secure a patent or an invention that provided a solution to a long felt need. This is contrary to the well established principle that the failure of others to provide a feasible solution to a long standing problem is probative of nonobviousness. *In re Piasecki*, 745 F.2d 1468, 1473-75, 223 USPQ 785, 790 (Fed.Cir.1984).

Applicants have provided evidence that the FDA and the American Association of Blood Banks (AABB) have been pushing for a safe and effective test for bacterial contamination of blood since the 1990s. Despite the urgency and attention devoted to this issue no test is currently available. In 1992, Ann Hoppe of the FDA stated that "although numerous studies have been performed by the FDA and others, no rapid and reliable test exists that could be readily applied in the blood bank setting." In 1996, similar sentiments were expressed by Svoboda et al to the Institutional Members of the AABB: major emphasis should be given to developing and evaluating practical, sensitive and specific screening assays for the detection of bacteria in platelet concentrates and to developing methods to decontaminate cellular blood components. In 1999, FDA Commissioner Henney testified before Congress about the concerns regarding bacterial contamination of blood. In 2001, Jacobs et al. again discuss the fact that bacterial contamination has been difficult to eradicate. Finally, as late as March 2003, the AABB, has

stated that "the blood bank or transfusion service shall have a method(s) to detect bacterial contamination in all platelet components." See www.aabb.org. These documents clearly show the state of the art and the long-felt need for a safe and effective blood screening protocol for bacterial contamination.

The Examiner dismisses these documents as merely implying that there are associated disadvantages with the currently available protocols. Applicant's disagree. The attention focused on this problem by the FDA and the AABB in the past ten years is a clear indication that despite the critical need to develop such a screening protocol, none exists. Eight-ten years have gone by since the publication of the references cited by the Examiner yet the skilled artisan has not modified the teachings of the art as proposed to develop a useful screening protocol. This is contrary to the well established principle stated in Piasecki that the failure of others to provide a feasible solution to a long standing problem is probative of nonobviousness.

Finally, the Examiner argues that the "using the method to determine when to transfer blood to a donor does not provide patentable weight." The Examiner goes on that " a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." The Examiner's reliance on Gurley is misplaced because the instant claims are directed to a method and not a composition.

To conclude, Applicants respectfully submit that the above rejection fails to establish a *prima facie* case of obviousness. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

5. Claims 2 and 15 are asserted as allegedly being unpatentable over Chan, McLaughlin and Tadler et al., as applied to claims 1 and 14 above, and further in view of Chang et al. for reasons of record. Applicants respectfully traverse this rejection.

Applicant's position regarding the Chan, McLaughlin, and Tadler et al. references has been stated *supra*. Applicant reiterate that Chang is directed to the safety of transfer of modified hemoglobin blood substitutes (see column 4 at lines 10-30), not to a method of screening

blood/blood product for bacteria and found to be free of gram positive and gram negative bacteria for transfusions, nor is it even directed to the detection of bacteria at all.

As stated above, Chan, McLaughlin, and Tadler et al. do not render claims 1-14 obvious and the deficiencies of these references is not cured by Chang which does not even teach detection of bacteria.

Therefore, the Chang patent does not make up the deficiencies of the Chan, McLaughlin, and Tadler et al. references, each of which have their own deficiencies as described *supra*. Reconsideration and withdrawal of this rejection is respectfully requested.

6. Claim 7 is asserted as allegedly being unpatentable over Chan (EP 461,462) in view of Tadler et al. (*J. of Clin. Lab. Anal.* 1989; 3: 21-25) under 35 USC 103(a). Applicants respectfully traverse this rejection.

As discussed above, the skilled artisan would not be motivated to modify Chan's immunoassay by using Tadler et al.'s antibodies because Chan is directed to a diagnostic method requiring specificity in the antibodies for the infectious agents to be detected. Therefore, it is unlikely that the skilled artisan would modify the Chan method; furthermore it is unlikely that the skilled artisan would select the Tadler antibodies for a screening method to detect clinically relevant amounts of bacteria in view of the teachings of the Tadler reference when taken as a whole. Applicants respectfully request withdrawal of the rejection based on the arguments set forth herein.

7. Claims 8 and 18 are asserted as being unpatentable over Chan in view of McLaughlin for the reasons of record. Applicants respectfully traverse this rejection.

The Examiner's position and Applicant's rebuttal with respect to the Chan and McLaughlin references have been discussed *supra*. As discussed above, the skilled artisan would not be motivated to modify Chan's immunoassay by using McLaughlin.'s antibodies because Chan is directed to a diagnostic method requiring specificity in the antibodies for the

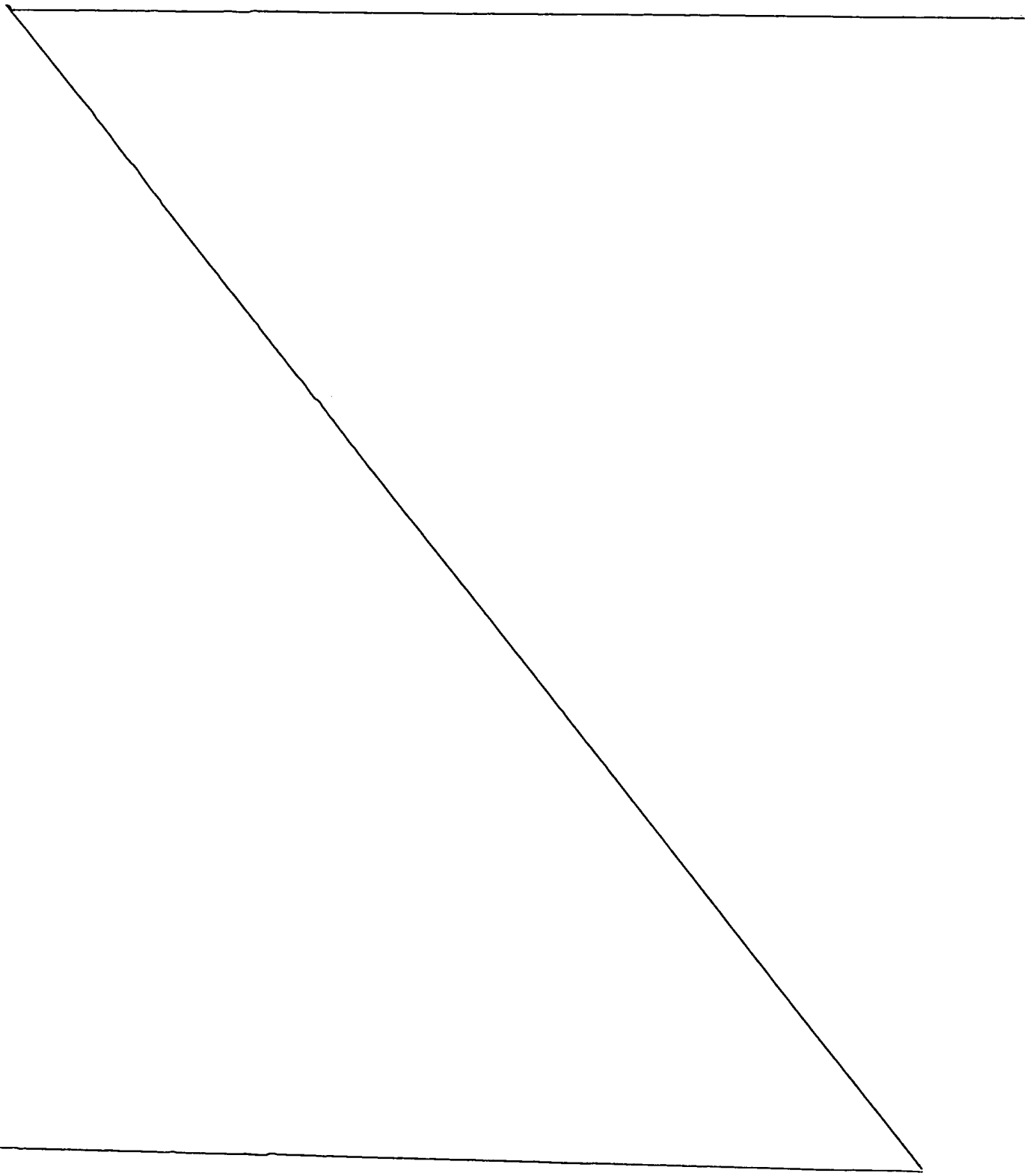
infectious agents to be detected. Therefore, it is unlikely that the skilled artisan would modify the Chan method; furthermore it is unlikely that the skilled artisan would select the McLaughlin antibodies for a screening method to detect clinically relevant amounts of bacteria in view of the teachings of the McLaughlin reference when taken as a whole.

Applicants respectfully request withdrawal of the rejection based on the arguments set forth *supra*.

8. Claims 23-25 are rejected under 35 USC 112, first paragraph as containing subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner states that the claims recite an antigen-binding fragment and a small molecule. Applicants respectfully disagree; the application teaches the use of antigen binding fragments such as Fab. Therefore, the specification conveys to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. Similarly, the specification sets forth specific small molecules, once again showing that the inventors has possession of the claimed invention. However, in an effort to expedite prosecution and not in acquiescence to the rejection, applicants hereby amend the claims to delete references to antigen binding fragments and small molecules.

9. Claims 24 is rejected under 35 USC 112, first paragraph as allegedly containing subject matter which was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. In particular, the Examiner states that the specification does not provide support "for a method that binds gram negative bacteria wherein an antibiotic, not vanomycin can be used as a binding agent of gram negative bacteria." Solely in an effort to expedite prosecution and not in acquiescence to the rejection, claim 24 is hereby canceled.

Applicants reserve the right to prosecute any canceled subject matter in a future application and respectfully request reconsideration and withdrawal of the rejection based on the arguments set forth *supra*.



MARKED-UP COPY OF THE CLAIMS

The amendments to the claims presented above incorporate changes as indicated by the marked-up versions below. Deleted material is indicated by a bracket and added material is underlined. For the examiner's convenience, a copy of all of the pending claims are provided, whether amended or not.

23. (Amended) The method of any of claims 1, 7, 14, and 17, wherein the set of binding agents that selectively bind Gram-positive bacterial antigens is selected from the group consisting of an antibody, [~~an antigen-binding fragment thereof, a small molecule~~,] an antibiotic, mannose binding protein (MBP), Toll-Like Receptor 2 (TLR-2), and histatins.

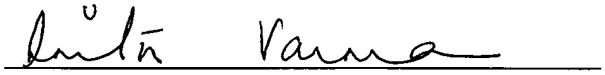
25. (Amended) The method of claim [24] 23, wherein the antibiotic is polymixin or bacitracin.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: April 11, 2003



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